DETAILED ACTION

Summary

1. Receipt of Applicant's Arguments/Remarks, amended claims and RCE filed on 01/07/08 is acknowledged.

Claims 1, 22, 23, 27, 39 and 40 have been amended. Claims 2-4 and 13 remain cancelled. New claims 42-61 have been added. Accordingly, claims pending in this application are **1, 5-12 and 14-61.**

Claim Objections

2. The amended claims 1, 27 and 42 have been written in an incorrect Markush language. The phrase "wherein the pathological condition is selected from **a",** shall be written as "wherein the pathological condition is selected from **the**". Examiner points to the following cited in MPEP.

> A Markush-type claim recites alternatives in a format such as "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925). The members of the Markush group (A, B, and C in the example above)

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

4. Claims 1, 5-12 and 14-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

5. Claims 1, 27 and 42 recite various moieties. The instant specification only provides few examples and recites only few specific moieties used to treat a pathological condition of an ocular tissue. Based on the instant disclosure, it obvious that the applicant was not in possession of all kinds of lipid, sulfates, sulfonates, phosphates, lipids, phospholipids, carboxylates, sulfosuccinates, arginine esters, cholesterol esters, carbamates, and ketals or the moieties in structure 1 attached to each and every therapeutic agent which one skilled in the art would be aware of. Additionally applicant claims treating a pathological condition of ocular tissue, comprising contacting a therapeutically active complex with ocular tissue. Recourse to the specification does not disclose forming therapeutic complex with any/each or every possible therapeutic agent. There are only few agents that are described which have been used in the invention. As such, by providing broadest reasonable interpretation to the claim, claims as recited can be read on forming complex with any therapeutic agent

particularly in the absence of specific recitation of specific agents which the applicant used at the time of invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).
To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states,

"An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus (therapeutic agents and several moieties claimed. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

6. Claim 1, 5-12 and 14-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

7. Claims 1, 22, 23, 27, 39, 40, 42, 59 and 60-61 recite the limitations "moieties

selected from a group consisting of sulfates, sulfonates, phosphates, lipids, phospholipids,carboxylates, sulfosuccinates, arginine esters, cholesterol esters, carbamates, carbonates, ketals, and the moiety having structure (I): or do not recite the moieties at all.

The specification discloses only certain moieties. In the absence of specific components and compounds as described under specific moieties and given the wide presence of various lipids, phospholipids, carbonates and other moieties that exist in the chemical and pharmaceutical field, the disclosure as presented would entail one skilled in the art to undergo undue experimentation in order to make and use the invention. Similarly in the absence of specific therapeutic agents, one skilled in the art would undergo undue experimentation to practice the claimed invention with each and every possible therapeutic agent in treating ocular condition. Claims 1, 22, 23, 42, 59 and 60-61 as recited, read on any therapeutic agent forming complex with any lipid or any other moieties. However, the specification only discloses few examples and species.
The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988).

Due to the large quantity of experimentation necessary to determine the efficacy of complexed moiety in any species of therapeutic agent, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the breadth of the claims, which fail to recite any particular active agent and any specific moiety undue experimentation would be required of the skilled artisan to make and/or use the claimed invention directed towards a method in treating a pathological condition of ocular tissue.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 5-12 and 14-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 1, 27 and 42 disclose the moiety as shown in structure 1, however, the nature of the complex formation is not disclosed. The moiety is attached at the hydrophobic end or lipophilic end? Also the position where the active agent is complexed with the moiety as shown in structure 1 is not clear from the drawn structure. The recitation of the limitation "optionally makes the claim indefinite since it is not clear if the limitation is really the limitation or not. Examiner suggests reciting claim in a clear and concise manner , distinctly claiming and pointing to the claimed subject matter.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1, 5-12, 14-15, 22-52 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (Feb. 2002) (herein onwards Cheng et al. I). (Investigative Ophthalmology & Visual Science, Feb. 2002, Vol. 43).

Cheng et al. disclose the intraocular drug delivery system using the free crystalline lipid prodrug of ganciclovir, HDP-P-GCV, as a prototype. Cheng et al. discloses a local intravitreal drug administration for vitreoretinal diseases, which bypasses the blood-ocular barriers and allows higher intraocular drug levels and avoids many side effects associated with systemic therapy. The intraocular drug delivery may also provide constant and slow release drug. Cheng et al. further disclose that surgical placement and replacement of intravitreal implants can cause significant adverse effects, including vitreous hemorrhage, retinal detachment, and endophthalmitis. Cheng et al. disclose that the intravitreal injection of a long-acting drug preparation would be less invasive than surgery and thus in order to prove such, Cheng et al. have demonstrated in the article that crystalline HDP-P-GCV in the form of 8- to 43-micrometer particles may

have utility in treating or preventing HSV retinitis when injected intravitreally as Infrequently as once a month or less frequently (see page 515, paragraph, 5 and column 2, first paragraph). The local retinal or lens toxicity observed with high doses may be eliminated, and antiviral duration could even be prolonged by using smaller drug particles, which may provide a better release rate and require less drug to maintain a therapeutic vitreous level with the advantage of a smaller drug depot (see page 521, 4th paragraph and column 2, first paragraph).

Because cheng's references teach that surgical placement and replacement of intravitreal implants can cause significant adverse effects, including vitreous hemorrhage, retinal detachment, and endophthalmitis. Cheng et al. disclose that the intravitreal injection of a long-acting drug preparation would be less invasive than surgery and thus in order to prove such, Cheng et al. have demonstrated in the article that crystalline HDP-P-GCV in the form of 8- to 43-micrometer particles have utility in treating or preventing HSV retinitis when injected intravitreally as infrequently as once a month or less frequently (see page 515, paragraph, 5 and column 2, first paragraph). Retinitis can be characterized as one of the conditions of eye trauma, therefore Cheng's references renders the claimed limitations obvious.

13. Claims 1, 5-12, 14-15, 22-52 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (May 2000). (Investigative Ophthalmology & Visual Science, May 2000, Vol. 41, No. 6).

Cheng et al. disclose that Cytomegalovirus (CMV) infection of the retina is the

most common infection in acquired immune deficiency syndrome (AIDS) patients. (See page 1523, first paragraph).

Ganciclovir (GCV) was the first drug to be approved for CMV infection in AIDS patients. Ganciclovir is effective in treating CMV retinitis by intravenous administration, but the drug does not eliminate the virus from the retina, requiring long-term suppressive maintenance therapy. Systemic toxicity such as bone marrow suppression was also a problem. The sustained-release GCV implant is effective treatment for CMV retinitis and recurrent CMV retinitis, but complications from surgery such as endophthalmitis and retina detachment are sight threatening. Therefore, in an effort to overcome the disclosed threat, Cheng et al. developed a simple, in-office injectable local therapy that would be effective, minimally toxic, and long-lasting for treatment of CMV retinitis (page 1523, column 2, paragraph 2 and 3).

Cheng et al. further disclose the experimental treatment efficacy of 1-O-hexadecylpropanediol-3-phospho-ganciclovir (HDP-P-GCV (see figure 1 and section under pathologic evaluation of the retinisis, page 1524) and disclose that the antiviral agent, HDP-P-GCV, may be very useful as a local therapy for treating CMV retinitis, HSV retinitis, and other intraocular viral infections in both immunocompromised and immunocompetent individuals. This type of self-assembling liposomal prodrug provides a prototype for intraocular drug delivery and may be applied to the delivery of many currently available drugs for chorioretinal or vitreoretinal diseases (page, 1531, last paragraph).

Because Cheng's references discloses the experimental treatment efficacy of 1-O-hexadecylpropanediol-3-phospho-ganciclovir (HDP-P-GCV (see figure 1 and section under pathologic evaluation of the retinisis, page 1524) and disclose that the antiviral agent, HDP-P-GCV, may be very useful as a local therapy for treating CMV retinitis, HSV retinitis, and other intraocular viral infections in both immunocompromised and immunocompetent individuals. Retinitis can be characterized as one of the conditions of eye trauma, therefore, Chengs references renders the claimed limitations obvious.

14. Claims 16-21 and 53-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cheng et al.) or (Cheng et al. I); (Investigative Ophthalmology & Visual Science, May 2000, Vol. 41, No. 6 and Feb. 2002, Vol. 43) as cited above in view of Unger (US Patent No. 6,120,751).

The teachings of Cheng et al. have been discussed above. Cheng et al. do not exclusively teach various nucleosides, antibody or AZT.

Unger discloses compositions comprising charged lipids, targeting ligands and the use of such compositions in drug delivery, targeted drug delivery, therapeutic imaging and diagnostic imaging as well as their use as contrast agents (abstract). The composition comprises various nucleosides, antibody, polyclonal antibody, fab fragments and AZT (column 45 and 46, lines 67 and 1 and column 48, lines 18-25).

It would have been obvious to the one of ordinary skilled in the art at the time the invention was made to incorporate various therapeutic agents such as various nucleosides as cited above in the formulation of Cheng et al. since Cheng et al. suggest

that assembling liposomal prodrug provides a prototype for intraocular drug delivery and may be applied to the delivery of many currently available drugs for chorioretinal or vitreoretinal diseases and Unger teaches that such a composition comprising nucleosides help in targeted delivery. A skilled artisan would have had a reasonable expectation of success in treating pathological condition of ocular tissue with a composition comprising therapeutic agents such as nucleosides.

Response to Arguments

15. Applicant's arguments with respect to claims 1, 5-12 and 14-61 have been considered but are moot in view of the new ground(s) of rejection.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580.

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more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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